Virginia Department of Health
Tularemia: Guidance for Healthcare Providers
Key Medical and Public Health Interventions after Identification of a Suspected Case

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1. Epidemiology

Tularemia is a zoonotic bacterial disease caused by the bacterium *Francisella tularensis*. *F. tularensis* is designated as a Category A agent (i.e., can be easily disseminated or transmitted with a higher rate of mortality than Category B agents). *F. tularensis* is also designated as a select agent, which means it could be developed as a bioterrorism agent and possession, use or transfer of the organism requires registration with CDC.

There are 3 subspecies of *F. tularensis* with differing virulence that cause disease among humans: *F. tularensis* ssp. *tularensis* (type A), ssp. *holartica* (type B) and ssp. *novicida*. The most virulent form, *Francisella tularensis* ssp. *tularensis,* is found only in North America. The case-fatality rate of type A infection, before the introduction of appropriate antimicrobials, is up to 30%. If appropriate antibiotic therapy is provided, the case-fatality rate is low. Two distinct groups of Type A have been identified: Group A. 1 (found in the central U.S. and California) and Group A. II (found in the western U.S. at higher elevations). *F. tularensis* ssp. *holartica* is referred to as Type B. This form of *F. tularensis* is more prevalent and is less virulent than Type A. Patients with Type B infection recover, even without treatment, with few fatalities. *F. tularensis* ssp. *novicida* is the rarest form and is associated with the mildest presentation. It is typically associated with waterborne-acquired infections.

F. tularensis is widespread throughout the Northern hemisphere. In the United States, naturally-occurring infections have been reported from all states except Hawaii. However, it is most common in the south central United States, the Pacific Northwest, and parts of Massachusetts.

Transmission of *F. tularensis* occurs primarily via tick or deer fly bites or handling infected animals. In the U.S., several different types of ticks (e.g., dog tick, wood tick and lone star tick) can transmit tularemia to humans. Deer flies have been shown to transmit tularemia in the western U.S. Infections due to tick and deer fly bites usually take the form of ulceroglandular or glandular

tularemia. *F. tularensis* can be transmitted to humans via inoculation of the skin, conjunctival sac, or oropharyngeal mucosa with contaminated water, blood or tissue when handling infected animal carcasses. In particular, this can occur when hunting or skinning infected rabbits, muskrats, prairie dogs and other rodents or performing necropsies. Other animals are susceptible to tularemia, including domestic cats and pet hamsters. Infection due to handling animals can result in glandular, ulceroglandular and oculoglandular tularemia. Oropharyngeal tularemia can result from eating under-cooked meat of infected animals.

Other means by which humans may be exposed to and acquire tularemia include inhaling dust or aerosols contaminated with the bacteria. This type of exposure would most likely occur during farming or landscaping activities, especially when machinery, such as mowers or tractors, runs over infected animals or carcasses. This type of exposure is rare, but may lead to pneumonic tularemia. Water may also become contaminated with *F. tularensis* via exposure to infected animals. Humans who drink contaminated water that has not been treated may contract oropharyngeal tularemia. *F. tularensis* is highly infectious when grown in culture and laboratory-acquired infections have been documented. Annually, approximately 100-150 cases are reported in the U.S. and 2 cases are reported in Virginia.

2. Clinical Manifestations

The incubation period for tularemia is usually from 3–5 days. The range is 1–14 days. Symptom onset is abrupt and influenza-like, with high fever (as high as 104^{o}F), chills, fatigue, generalized body aches, headache and nausea.

Tularemia is characterized by several distinct forms:

- Ulceroglandular: occurs following a tick or deer fly bite or after handling of an infected animal; cutaneous ulcer at site where the organism entered the body with regional lymphadenopathy; most common syndrome
- Glandular: generally acquired through the bite of an infected tick or deer fly or from handling sick or dead animals; regional lymphadenopathy with no ulcer; common syndrome
- Oculoglandular: occurs when the bacteria enter through the eye and may occur during butchering of an infected animal and touching of eye occurs; conjunctivitis with preauricular lymphadenopathy; less common syndrome
- Oropharyngeal: occurs from eating or drinking contaminated food or water; stomatitis or pharyngitis or tonsillitis and cervical lymphadenopathy; less common syndrome
- Intestinal: intestinal pain, vomiting and diarrhea
- Typhoidal: febrile illness without early localizing signs and symptoms; less common syndrome
- Pneumonic: most serious form of tularemia, occurring after intentional release of organism, breathing in dusts or aerosols containing the organism or other forms of disease are left untreated and the bacteria spread through the bloodstream to the lungs; primary pleuropulmonary disease

3. Specimen Collection and Laboratory Testing

Protocols for sentinel clinical laboratories are no longer posted on the CDC website. The American Society for Microbiology (ASM) has agreed to take the lead in the development and dissemination of sentinel laboratory information. The most current ASM guidelines for specimen collection and laboratory testing for tularemia are available at http://www.asm.org/index.php/guidelines/sentinel-

guidelines. For additional laboratory guidance, refer to the CDC Infectious Diseases Test Directory or CDC's Biosafety in Microbiological and Biomedical Laboratories (5th edition) (see References).

Laboratory personnel **must** be alerted if tularemia is suspected, so that appropriate precautions can be taken. Diagnostic procedures with clinical materials can be performed in biosafety level (BSL) 2 conditions. All work with suspect cultures of *F. tularensis* should be done in a biological safety cabinet. Manipulation of cultures and other procedures that might produce aerosols or droplets (e.g., grinding, centrifuging, vigorous shaking, animal studies) should be conducted under BSL 3 conditions. Because of the highly infectious nature of *F. tularensis*, consultation with the state public health laboratory, Division of Consolidated Laboratory Services (DCLS), is strongly recommended. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617. Sample collection instructions for testing at DCLS are shown in Table 1.

Table 1. Sample Collection Instructions for Testing Suspected Tularemia at DCLS/CDC*

Test	Acceptable samples	Amount	Instructions
Florescent Antibody (FA) test OR Polymerase Chain Reaction (PCR) test	Tissue: Biopsy of ulcer or wound; autopsy tissue	1 gram	Place in sterile container; moisten with sterile broth or saline. Ship to lab immediately at room temperature; if more than 2 hours, freeze and ship on dry ice.
	Lymph node aspirate	1-2 cc	Ship to lab immediately; if more than 2 hours, refrigerate.
Serology (only performed at CDC)	Serum	Acute and convalescent (14 days apart)	Collect in red top or tiger top tube. Remove serum and place in sterile tube, then store frozen.
Bacterial isolate from culture	Blood, skin, ulcers, lymph node drainage, gastric washings or respiratory tract secretions		Ship suspicious isolates (tiny Gram-negative coccobacilli) on slant (preferred) or agar plate at room temperature

*If tularemia is suspected, notify the local health department immediately to discuss the case and laboratory testing (see www.vdh.virginia.gov/LHD/index.htm). Specimens should be sent to Division of Consolidated Laboratory Services (DCLS) after LHD has been consulted and testing has been approved by LHD/DCLS. The DCLS Emergency Duty Officer can be reached 24/7 at (804) 335-4617.If multiple types of specimens are being shipped to DCLS, use cold packs for shipment. In addition, the DCLS Blood and Body Fluid Submission Form should be completed with the appropriate test request.

4. Diagnosis

The current CDC case definition for tularemia is available at http://wwwn.cdc.gov/nndss/script/casedefDefault.aspx. Note that a case definition is set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions, and should not be used by healthcare providers to determine how to meet an individual patient's health needs.

5. Treatment

Recommendations for tularemia treatment are summarized in Table 2. Those who develop an unexplained fever or flu-like illness within 14 days of presumed exposure should begin standard treatment. Antibiotics used to treat tularemia include streptomycin, gentamicin, doxycycline and

ciprofloxacin. Treatment usually lasts 10 to 21 days depending on the stage of illness and the medication used. Although symptoms may last for several weeks, most patients completely recover.

Table 2. Tularemia treatment[1] recommendations for cases*

Adults (excluding pregnant women) Preferred Choices: • Streptomycin, 1 g IM twice daily or • Gentamicin, 5mg/kg IM or IV once daily[3] Alternative Choices: • Doxycycline, 100mg IV twice daily or • Ciprofloxacin, 400 mg IV twice daily[3]
Pregnant Women Preferred Choices: • Streptomycin, 1 g IM twice daily or • Gentamicin, 5 mg/kg IM or IV once daily[3] Alternative Choices: • Doxycycline, 100 mg IV twice daily or • Ciprofloxacin, 400 mg IV twice daily

Children
Preferred Choices:
• Streptomycin, 15 mg/kg IM twice daily (should not exceed 2 gm/d) or
• Gentamicin, 2.5 mg/kg IM or IV 3 times daily[3]
Alternative Choices:
• Doxycycline,
  ○ If weight ≥ 45 kg, 100 mg IV
  ○ If weight < 45 kg, give 2.2 mg/kg IV twice daily or
• Ciprofloxacin, 15 mg/kg IV twice daily[2]

*For additional information on dosing, please consult with the package inserts. For additional guidance on treatment, refer to Dennis DT, et al 2001 (http://www.bt.cdc.gov/Agent/Tularemia/TularemiaConsensus.pdf) and Adalja AA, et al 2015 (http://www.nejm.org/doi/pdf/10.1056/NEJMra1409755)

[1]Treatment with streptomycin, gentamicin or ciprofloxacin should be continued for 10 days; treatment with doxycycline should be continued for 14–21 days. Persons beginning treatment with IM or IV doxycycline, ciprofloxacin, or chloramphenicol can switch to oral antibiotics when clinically indicated.

[2]Ciprofloxacin dosages should not exceed 1 g/d in children.

[3]*The US Food and Drug Administration has not approved all treatment regimens shown in the chart.*

6. Postexposure Prophylaxis

Recommendations for tularemia postexposure prophylaxis (PEP) are summarized in Table 3. If a known biological attack using *F. tularensis* has occurred and exposed persons are identified during the incubation period (before they become ill), then individuals should receive prophylactic treatment with 14 days of oral doxycycline or ciprofloxacin as outlined in Table 3. If an attack is discovered only after some individuals become ill, persons potentially exposed should begin surveillance for a fever. Postexposure prophylactic treatment of close contacts of tularemia patients is not recommended because person-to-person transmission is not known to occur. Laboratory personnel potentially exposed to the agent should be assessed on a case-by-case basis. For high-risk exposures, including needle stick, spill, centrifuge accident, sniffing a culture plate, or conducting procedures that generate aerosols, prophylaxis should be given. For these and other exposures, the local health department should be consulted to help assess the risk and conduct surveillance (in conjunction with DCLS).

Table 3. Postexposure prophylaxis (PEP)[1] and monitoring recommendations for tularemia exposures* (*Regimens may also be used for treatment in severe circumstances when standard IM or IV treatment is impractical or unavailable*)

Adults (excluding pregnant women) Preferred Choices: Doxycycline, 100 mg orally twice daily or Ciprofloxacin, 500 mg orally twice daily[3]
Pregnant Women Preferred Choices: Doxycycline, 100 mg orally twice daily or Ciprofloxacin, 500 mg orally twice daily
Children Preferred Choices: Doxycycline, • If weight ≥ 45 kg, give 100 mg orally twice daily • If weight < 45 kg, give 2.2 mg/kg orally twice daily or Ciprofloxacin, 15 mg/kg orally twice daily[2]

*For additional information on dosing, please consult with the package inserts. For additional guidance, refer to: Dennis DT, et al 2001 (http://www.bt.cdc.gov/Agent/Tularemia/TularemiaConsensus.pdf) and Adalja AA, et al 2015 (http://www.nejm.org/doi/pdf/10.1056/NEJMra1409755).

[1]The duration of all recommended therapies for prophylaxis and treatment in severe circumstances when IM or IV treatment is not available is 14 days.

[2]Ciprofloxacin dosages should not exceed 1 g/d in children.

[3]*The US Food and Drug Administration has not approved all treatment regimens shown in the chart.*

7. Vaccination

Until recently, a vaccine has been available to protect laboratorians routinely working with *F. tularensis*. This vaccine is currently under review by the US Food and Drug Administration (FDA) and is not generally available in the United States.

8. Infection Control

Standard precautions should be used for managing patients and handling clinical materials. Tularemia is not known to be spread from person to person. People who have tularemia do not need to be isolated.

9. Decontamination

Persons with direct exposure to powder or liquid aerosols containing *F. tularensis* should wash body surfaces with soapy water. Standard levels of chlorine in water should protect against waterborne infection. Clothing or linens contaminated with body fluids of patients with tularemia should be disinfected per standard hospital procedure.

Following an intentional release of *F. tularensis*, the risk to humans of acquiring tularemia from infected animals or arthropod bites is considered minimal and could be reduced by avoidance of sick or dead animals and by using protective measures against biting arthropods.

10. Postmortem Practices

If tularemia is suspected as a cause of death, the district Office of the Chief Medical Examiner should be notified immediately (see http://www.vdh.virginia.gov/medExam/ContactUs.htm). Bodies of patients who die of tularemia should be handled using standard precautions, but autopsy procedures likely to produce aerosols or droplets should be avoided.

11. Public Health Measures

- Suspected or confirmed tularemia cases should be reported immediately to the local health department. See http://www.vdh.virginia.gov/LHD/index.htm.
- Tularemia is considered to be a potential agent for deliberate use, particularly if used as an aerosol threat. Cases presenting as primary pneumonia require prompt identification and specific treatment to prevent a fatal outcome.
- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation of agent and other studies after consultation and approval. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.
- Designated public health authority should begin an epidemiologic investigation immediately, including fever surveillance of individuals potentially exposed to *F. tularensis*.
  - Collect detailed information from the patient to identify the source of the exposure.
  - Investigate contacts of the case-patient for compatible illness to identify a potential common exposure.
  - Suspected food items (e.g. ingested contaminated wild game meat) should be collected for possible testing.
  - VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.
- Implement control measures to prevent disease and additional exposures.
  - For laboratorians or others potentially exposed who might have worked with the agent before identification as *F. tularensis*, PEP and postexposure monitoring might be recommended based on a risk assessment.
  - Advise residents to use care and wear gloves when handling sick or dead animals.
  - Advise residents to use insect repellent containing DEET (N,N-diethyl-m-toluamide) on your skin, or treat clothing with repellent containing permethrin, to prevent insect bites.

12. References and Resources

Adalja AA, ~~;~~ Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. NEJM. 2015; 327 (10): 954-962. Available at http://www.nejm.org/doi/pdf/10.1056/NEJMra1409755 (accessed March 10, 2015).

American Academy of Pediatrics. Tularemia. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:256-258.

American Public Health Association. Tularemia. In: Heymann DL, ed. *Control of Communicable Diseases Manual*. 20th ed. Washington DC: American Public Health Association; 2015: 650-654.

American Society for Microbiology (ASM). Sentinel level clinical laboratory guidelines for suspected agents of bioterrorism and emerging infectious diseases: *Francisella tularensis*. Revised November 2014. Available at http://www.asm.org/images/PSAB/TularemiaNov2014.pdf (accessed December 10, 2014)

Centers for Disease Control and Prevention (CDC). Chosewood, LC and Wilson, DE eds. Biosafety in Microbiological and Biomedical Laboratories. 5th edition. HHS Publication No. (CDC) 21-1112, 2009. Available at http://www.cdc.gov/biosafety/publications/bmbl5/bmbl.pdf (accessed December 8, 2014).

Centers for Disease Control and Prevention (CDC). CDC Infectious Diseases Laboratories: Test Directory. Available at http://www.cdc.gov/laboratory/specimen-submission/list.html (accessed December 8, 2014).

Centers for Disease Control and Prevention (CDC). National Notifiable Diseases Surveillance System Case Definitions. Available at http://wwwn.cdc.gov/nndss/script/casedefDefault.aspx (accessed December 10, 2014).

Centers for Disease Control and Prevention (CDC). Tularemia. Available at http://www.cdc.gov/tularemia/index.html (accessed December 10, 2014).

Centers for Disease Control and Prevention (CDC). Tularemia: Managing Potential Laboratory Exposures. Available at http://www.cdc.gov/tularemia/laboratoryexposure/index.html (accessed December 10, 2014).

Dennis DT, Inglesby TV; Henderson DA, et al. Tularemia as a Biological Weapon: Medical and Public Health Management. *JAMA*. 2001;285(21):2763-2773.

Nelson C, Kugeler K, Petersen J, Mead P. Tularemia – United States, 2001-2010, *MMWR*. 2013; 62 (47); 963-966. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6247a5.htm (accessed December 10, 2014).

Young, EJ. Francisella tularensis. In: Mandell GL, Bennett JE, Dolin R, ed. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia, PA: Churchhill Livingstone Elsevier; 2010: 2927-2937.